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A new sulcus-corrected approach for assessing cerebellar volume in spinocerebellar ataxia

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ABSTRACT

Precise volumetry of the cerebellum still remains challenging, due to thin sulci and gyri. We present a new fast and reliable sulcus-corrected approach for quantitative assessment of cerebellar atrophy, evaluated on patients with spinocerebellar ataxia (SCA). Thin-sliced T1-weighted magnetic resonance images (MPRAGE) were acquired in 11 genetically confirmed SCA6 patients and in a group of age-matched control subjects ($n=14$). Post-processing involves a morphological image segmentation pipeline as a basis for a sulcus-corrected cerebellar volume measurement. Cerebellar volumes and intra-rater, inter-rater and scan–rescan reproducibility were quantified. Reliability of the measurements was validated using an anatomical preparation of the cerebellum. Repeatability coefficients (RC: intra-rater/inter-rater/scan–rescan) of the method were 1.07%/1.11%/1.35%. Absolute cerebellar volumes showed good agreement with the actual volume of the anatomical preparation. The cerebellar volume of the SCA 6 was 96.3 ± 12.1 ml (mean ± S.D.), which was significantly lower than the results of the corresponding control groups. The cerebellar volume correlated significantly to clinical dysfunction in SCA6. This is the first study to demonstrate the feasibility of a new sulcus-corrected approach to assess cerebellar volume. In contrast to currently used methods, this new approach may be more sensitive even to small atrophic changes affecting sulcal widening.

1. Introduction

Quantitative assessment of structures in the central nervous system (CNS) has become a field of significant interest in neuroscience. In neurodegenerative diseases, volumetric magnetic resonance imaging (MRI) measurements are widely used to monitor disease progression and treatment effects over time. Besides global measurements of whole brain volumes, regional analysis of smaller structures is important, especially if the pattern of atrophy is more restricted to few or single CNS areas, such as the cerebellum. The cerebellum itself is morphologically very complex. Although the volume of the cerebellum is only 1/7 of the cerebrum, its surface area is almost that size of the size brain's hemisphere. Due to its thin sulci and gyri and its close connection to the brainstem, volumetric assessment of the cerebellum is challenging. Several strategies have been introduced for assessing cerebellar volume changes in cerebellar degeneration, evoked by spinocerebellar ataxias (SCA) (Klockgether et al., 1998; Luft et al., 1998; Murata et al., 1998a, 1998b; Satoh et al., 1998; Richter et al., 2005; Schulz et al., 2010) and other conditions, e.g. psychiatric disorders (Joyal et al., 2004), epilepsy (Hagemann et al., 2002), multiple sclerosis (Anderson et al., 2009) and age-related changes (Luft et al., 1997; Luft et al., 1998; Raz et al., 2001). Since planimetric and manual outline measurements (Murata et al., 1998a; Murata et al., 1998b; Raz et al., 2001; Joyal et al., 2004) are time-consuming and not always an objective measurement, semi-automated and fully automated techniques based techniques based on 3D datasets have been developed for measuring cerebellar volume (Luft et al., 1998; Satoh et al., 1998; Richter et al., 2005). Compared to 2D methods, these 3D techniques are characterized by a higher accuracy. Additionally, they are relatively independent to the exact positioning of the patient during the MR examination.

So far, these techniques do not incorporate all atrophy-related changes. Specifically early signs, such as the widening of the sulci, are not assessed by the majority of techniques, e.g. by excluding sulcus indentations (Murata et al., 1998a, 1998b; Richter et al., 2005) or by not including all available MR slices for cerebellar volume estimation (Hagemann et al., 2002).

Spinocerebellar ataxias (SCA) compromise a group of clinically and genetically heterogeneous autosomal dominantly inherited disorders characterized by progressive ataxia (Schöls et al., 2004). SCA6 is one of the most common subtypes. The disease is defined by CAG repeat expansions in the corresponding CACNA1A gene (Zhuchenko et al., 1997; Schöls et al., 2004). Recent data suggest that in SCA6 the degenerative process is limited to the cerebellum (Takiyama et al., 1994; Takahashi et al., 1998; Rub et al., 2004). Therefore, this SCA subtype, with a pure cerebellar degeneration leading to clinical

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disability, seems to be a promising disease entity to demonstrate the value of a MRI surrogate marker by means of cerebellar volumetry.

The aims of the current study were two-fold: 1) to implement and validate an image processing system including a sulcus-corrected analysis step for quantitative volumetric analysis of the cerebellum and 2) to correlate cerebellar volumes in a group of SCA6 patients with their clinical status to confirm the suitability of this method by comparison with previous findings. The reproducibility of the volume measurements as well as the reliability of the absolute results was tested by MR examinations of SCA6 patients, healthy controls and an anatomical preparation of the cerebellum.

2. Methods

2.1. Subjects

Eleven patients with genetically confirmed SCA6 were recruited from the ataxia outpatient clinic in Bochum and enrolled in this study. In addition, an age- and gender-matched group of 14 healthy volunteers without neurological impairment was enrolled. Disability was assessed according to the International Cooperative Ataxia Rating Scale (ICARS) (Trouillas et al., 1997). Detailed description of the study groups is provided in Table 1. The study was approved by the local Medical Ethics Committee (Ethical committee of the Ruhr-University of Bochum, Germany). All individuals gave their written informed consent to participation in the study.

2.2. Data acquisition

High-resolution T1-weighted 3D MRI data (MPRAGE) were acquired with a 1.5 T scanner (Magnetom Symphony™, Siemens, Erlangen, Germany). The imaging protocol comprised a high-resolution Turbo FLASH 3D sequence [repetition time, TR = 1900 ms; echo time, TE = 3.93 ms; 128 sagittal slices; matrix: 256 × 256; voxel size: 1 mm × 1 mm × 1.5 mm] covering the entire head of the subjects. A standard procedure according to outer anatomical markers was used to position the subjects within a standard head coil. The sagittal slices were defined using three orthogonal locator scans aligned to the longitudinal fissure, corpus callosum and brainstem (Fig. 1), so that the inferior boundaries of the corpus callosum were located in the isocenter. By this procedure, the whole cerebellum was situated inside the central area of the images, in order to diminish signal drop off by inhomogeneous coil characteristics especially in the inferior cerebellum.

2.3. Post-processing

For all patients and control subjects the 3D datasets were post-processed by using an efficient semi-automated method, which we refer to as “sulcus-corrected morphological cerebellar volumetry”.

Table 1
Demographic and clinical data.

	SCA6	Healthy controls
Number (f/m)	11 (6/5)	14 (6/9)
Age, years (mean ± S.D.[a])	66 ± 6	64 ± 6
Disease duration, years (mean ± S.D.[a])	8.9 ± 5.7	
Age of onset, years (mean ± S.D.[a])	56.9 ± 8.5	
ICARS[b] (mean ± S.D.[a])	29.5 ± 9.4	
CAG repeat length (mean ± S.D.[a])	21.9 ± 0.6	
Normal range[c]	<20	

[a] Mean : arithmetic mean value; S.D. : standard deviation.
[b] ICARS: score according to the International Cooperative Ataxia Rating Scale.
[c] http://www.geneclinics.org.

From a user perspective, segmentation and volumetry are performed as a sequence of three major steps (cf. Fig. 1A–C):

1. skull stripping,
2. cerebellum segmentation, and
3. histogram based volume computation.

While the third step is fully automated, the first two require limited user interaction. Therein, the user is required (step 1) to define a few include and exclude markers for skull stripping based on an interactive watershed transform (IWT, cf. below), and (step 2) the visual inspection and gross anatomical labeling through additional markers for cerebellum separation.

An overview of the post-processing pipeline with the three major steps plus two auxiliary steps (brain mask computation and cerebellum mask completion) for cerebellar volumetry is provided in Fig. 2. The complete pipeline and user interface were implemented within the software platform MeVisLab (http://www.mevislab.de). This platform comprises a rich set of standard image processing functionality and graphical user interface elements that can be efficiently combined and applied to clinical image data. The specific algorithms required for cerebellum segmentation were not included in MeVisLab, but we implemented them as new MeVisLab modules in accordance to the respective publications. The skull stripping method and IWT algorithm are explained in detail elsewhere (Hahn and Peitgen, 2000; Hahn and Peitgen, 2003). Snapshots of the user interface and of the underlying MeVisLab network are provided in Figs. 3 and 4, respectively.

In the following, we concentrate on explaining the mechanism of the overall sequence of post-processing steps:

2.3.1. Skull stripping

The skull stripping method isolates the brain including brainstem, spinal cord, CSF, ventricles, and intracerebral vessels from surrounding bright image elements, whereas the user can click on every object not belonging to the desired group of objects and add missing objects through exclude and include markers, respectively (module “InteractiveWatershed” in Fig. 4). It is important to note that a very high reproducibility between raters besides a high efficiency is achieved (Lukas et al., 2004) based on the fact that the markers are to be placed inside of objects, whereas the respective boundaries are computed automatically based on the marker input (Hahn and Peitgen, 2003). Time consuming slice-by-slice interaction or manual drawing of boundaries is completely avoided. In our study, fewer than 20 single include or exclude clicks were required for the skull stripping of a complete volume, which is a small interaction compared with the number of slices. After placement or deletion of any marker, the IWT is recalculated within a fraction of a second such that the resulting segmentation can be observed on three orthogonal views and iteratively be refined (Fig. 1B).

2.3.2. Computation of rough binary mask

After skull stripping, the goal of the second step is to isolate the cerebellum without any adjacent non-cerebellar bright image elements. Therefore, to gain optimal segmentation results, extra-cerebellar vessels close to the cerebellar surface and the cerebellar tentorium have to be marked explicitly by exclude markers already in the first step. From the resulting skull stripped volume, we first automatically compute a rough binary brain mask that serves as a basis for separating the cerebellum from cerebrum including brainstem and the upper spinal cord. This binary mask is generated by a heuristically adjusted 45-percentile threshold (modules “HistogramParameters” and “AutomatedThreshold” in Fig. 4) and typically includes the white matter and some of the partial-volume region between white and gray matter voxels (marker pixels in Fig. 1B). This fixed threshold was optimized during the development of the method. Note that this step is robust against minor